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Published in:
European Journal of Cancer

DOI (link to publication from Publisher):
10.1016/j.ejca.2019.08.033

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

European Journal of Cancer 127 (2020) 173–182

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

Vinflunine/gemcitabine versus carboplatin/gemcitabine as first-line treatment in cisplatin-ineligible patients with advanced urothelial carcinoma: A randomised phase II trial (VINGEM)

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Received 6 May 2019; received in revised form 6 August 2019; accepted 18 August 2019
Available online 22 October 2019

KEYWORDS
Bladder cancer;
Urothelial carcinoma;
Cisplatin-unfit;
Renal impairment;
Vinflunine;

Abstract ***Background:*** The present study (VINGEM) is the first randomised trial comparing vinflunine/gemcitabine (VG) to standard carboplatin/gemcitabine (CG) in patients with advanced urothelial carcinoma (aUC) ineligible for treatment with cisplatin.
Patients and methods: Patients with aUC, creatinine clearance 30–60 ml/min, performance status ≤1 and no prior chemotherapy for metastatic disease were randomised to the experimental arm (vinflunine 280 or 250 mg/m^2 day 1, gemcitabine 1000 mg/m^2 days 1 and 8, q21

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https://doi.org/10.1016/j.ejca.2019.08.033

Vinflunine/gemcitabine; Carboplatin/gemcitabine

days) or the control arm (carboplatin AUC 4.5 day 1, gemcitabine 1000 mg/m^2 days 1 and 8, q21 days). Primary end-point was progression-free survival (PFS).

Results: Sixty-two patients were randomised; a total of 59 patients were treated (29 VG, 30 CG). There was no significant difference in PFS between the treatment arms: median 6.2 months for VG versus 6.3 months for CG (hazard ratio [HR]: 0.75, 95% confidence interval [CI]: 0.44–1.28; $P = 0.293$). Median overall survival was 12.5 months for VG versus 10.6 months for CG. The overall response rate (ORR) was higher in the VG arm than in the CG arm (63% versus 40%) but was not statistically significant in the intention-to-treat analysis. Furthermore, VG showed a high complete response (CR) rate, 22% versus 3% in CG. In the per-protocol group, both ORR and CR were significantly higher for VG than for CG. The most common adverse events (AEs) were fatigue, haematological toxicities, gastrointestinal disorders and nausea/vomiting. Common grade III/IV AEs were neutropenia (VG 62%, CG 43%), thrombocytopenia (VG 7%, CG 37%) and febrile neutropenia (VG 31%, CG 7%).

Conclusions: The combination of VG did not improve PFS compared with standard treatment with CG in patients unfit for cisplatin due to renal impairment. The response rate of VG indicates, however, an active regimen and warrants further studies.

Clinicaltrials.gov number: NCT02665039.

1. Introduction

Since the late 1980s, cisplatin-based chemotherapy has been the standard treatment for locally advanced and metastatic urothelial cancer (aUC) [1–3]. However, up to 50% of patients with aUC are ineligible, or 'unfit', for cisplatin [4], either because of impaired renal function, low performance status or co-morbidity.

Thus far, the European Organisation for Research and Treatment of Cancer (EORTC) study 30986 represents the first and only reported randomised phase III trial including patients ineligible for cisplatin and comparing methotrexate, carboplatin and vinblastine (M-CAVI) with carboplatin and gemcitabine (CG) [5,6]. This study showed no significant differences between the treatment groups with regards to overall response rate (ORR; 41% with CG versus 30% with M-CAVI) or median overall survival (mOS; 9.3 versus 8.1 months), although there was a significant difference in severe acute toxicity in favour of CG. Based on this trial, CG is recommended as one standard first-line treatment for cisplatin-unfit patients with aUC [7,8].

Recently, immunotherapy with checkpoint inhibitors (ICIs) has proven efficacy in first-line treatment for cisplatin-unfit patients with aUC. Pembrolizumab [9] and atezolizumab [10] show in single-arm phase II trials an ORR of 24% and 23%, respectively, and the reported mOS for atezolizumab was 15.9 months. The use of ICIs is currently restricted to patients expressing high levels of programmed death-ligand 1 (PD-L1), approximately 30% [11] of the patients [12,13].

In 2009, the European Medicines Agency (EMA) approved the third-generation anti-microtubule inhibitor vinflunine as second-line treatment after platinum-based chemotherapy in patients with aUC, improving mOS for vinflunine compared with best supportive care in the eligible population (but not in the intention-to-treat [ITT] population) [14]. Furthermore, the efficacy of vinflunine in second-line treatment has been confirmed in real-world studies [15]. Vinflunine combinations, vinflunine and gemcitabine (VG) versus vinflunine and carboplatin, were explored as first-line treatment for cisplatin-unfit patients in the randomised phase II trial JASINT1 [16], showing promising response rates and survival (ORR 53% with confirmed ORR 44% and mOS 14.0 months in the VG arm), although the trial did not include a non-investigational control arm.

Based on available data on vinflunine as second-line treatment in patients with aUC and the potential benefit of vinflunine combination therapy as first-line treatment, we explored the efficacy of VG versus standard chemotherapy with CG in the randomised phase II VINGEM trial in patients with aUC unfit for cisplatin due to renal impairment.

2. Patients and methods

2.1. Study design

The randomised multicentre phase II trial VINGEM was conducted at 11 centres associated with the Nordic Urothelial Cancer Oncology Group (NUCOG) in Denmark, Finland and Sweden. The study protocol was approved by the EMA and by the national medicine agencies and independent ethics committees in each of

the participating countries. The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice, as well as with local laws and regulations. All patients provided written informed consent.

2.2. Patients

Eligible patients had histologically confirmed transitional cell carcinoma of the urothelial tract with evaluable locally advanced (T4bN0M0) or metastatic disease and impaired glomerular filtration rate (GFR) of 30–60 ml/min measured by Iohexol or Cr-ethylene diamine tetra-acetic acid (EDTA) clearance and Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 1. Prior chemotherapy was not allowed, except for perioperative platinum-containing chemotherapy given $\geq$6 months before disease relapse. The main exclusion criteria were any history of serious concurrent illness or uncontrolled medical condition, impaired bone marrow or liver function and other malignancies. Complete inclusion and exclusion criteria are given in the protocol (Supplementary Appendix).

2.3. Procedures

Patients were randomised 1:1 and stratified for ECOG PS 0 versus 1 and presence or absence of visceral metastases. Vinflunine was administered at 250 mg/m^2 (age > 80 years and/or GFR 30–40 ml/min) or 280 mg/m^2 (GFR 41–60 ml/min) on day 1 and gemcitabine at 1000 mg/m^2 on days 1 and 8, q21 days, or carboplatin AUC 4.5 was given on day 1 and 1000 mg/m^2 of gemcitabine on days 1 and 8, q21 days. Treatment continued until disease progression, unacceptable toxicity or patient withdrawal of consent.

Dose reduction and dose delay were permitted according to the protocol. Granulocyte colony-stimulating factor (G-CSF) was allowed when the per-protocol recommended dose modifications were insufficient.

2.4. Outcomes

The primary end-point was progression-free survival (PFS), defined as the time from randomisation to radiological disease progression or death. The secondary end-points were ORR, disease control rate (DCR), OS, toxicity and health-related quality of life (HRQoL). Radiological assessment was performed at baseline and every 6 weeks until progression by computer tomography or magnetic resonance imaging as per Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Objective responses were confirmed at the next scheduled radiological assessment or at an additional evaluation after 28 days if the treatment was terminated for any reason other than progression.

AEs were graded after every treatment cycle in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. HRQoL was assessed before randomisation, every 6 weeks during treatment, and at discontinuation of treatment using the 30-item EORTC Quality of Life Core Questionnaire (QLQ-C30, version 3.0) [17].

2.5. Statistical analysis

The study was designed as a randomised phase II screening trial, with PFS as the primary end-point [18]. The trial was initially intended to detect an increase in the median PFS from 5 to 7.5 months, requiring inclusion of 120 patients. In April 2016, owing to slow accrual rate, an amendment was approved to decrease the required number of patients to 60 to enable detection of an increase in median PFS from 5 to 9 months (with α = 10% and β = 20%).

PFS was compared between the treatment arms using the log-rank test at a significance level of 5%. Hazard ratios (HRs) were calculated using a Cox proportional-hazards model. The Kaplan-Meier technique was applied to estimate time-related end-points. Efficacy was evaluated according to the ITT principle comprising all randomised patients and in an additional analysis in the per-protocol population, i.e. excluding those patients who completed less than one treatment cycle. ORR and DCR were tested by the Fisher exact test. Descriptive statistics were used to assess safety for all patients who received at least one dose of study treatment. All items in the EORTC QLQ-C30 questionnaire were linearly transformed to functioning or symptom scales ranging from 0 to 100 according to the scoring manual [19]. The differences in HRQoL were analysed at baseline and after two treatment cycles, using linear regression models and scored with 99% confidence intervals (CIs) and with statistical significance set at $p \leq 0.01$. Statistical analyses were performed using STATA software, version 15 (StataCorp LLC, Texas, USA).

3. Results

3.1. Patients

Between April 2014 and February 2018, 62 patients were randomised to receive treatment with VG (n = 32) or CG (n = 30) (Fig. 1). Baseline characteristics were well balanced between the two arms (Table 1). At the cut-off time for data analysis (31 September 2018), no patients were on study treatment and 57 patients had progressed in their disease or died. The median follow-up duration was 21 months (range, 6–41 months) with 44 deaths. All patients were included in the ITT analysis (n = 62). Three patients in the VG arm were excluded in the per-

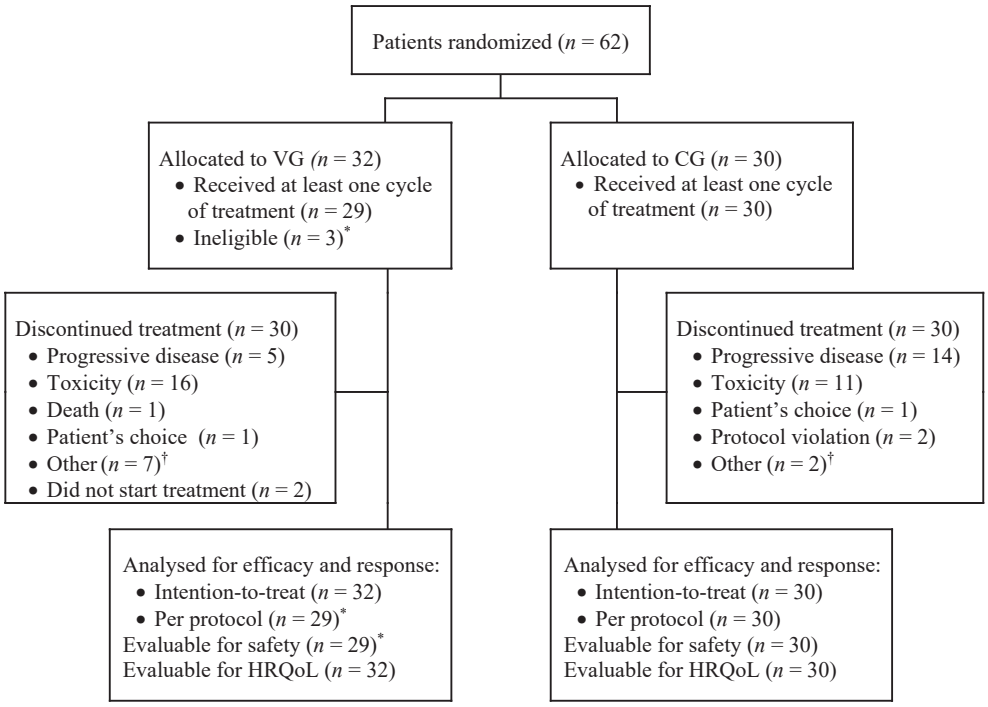

Fig. 1. CONSORT diagram. *Two patients were excluded because of adverse events before onset of treatment, one patient withdrew because of immediate local infusion site reaction upon the first exposure of vinflunine. †Investigator's decision due to local procedures after six cycles (six patients), complete response and no improvement of HRQoL (one patient), deterioration of performance status (one patient), stroke (one patient). VG, vinflunine and gemcitabine; CG, carboplatin and gemcitabine; HRQoL, health-related quality of life.

protocol analysis ($n = 59$): two were excluded because of AEs before onset of treatment (stroke and ileus) and one was excluded because of immediate local infusion site reaction upon the first exposure of vinflunine (withdrawn from further study treatment).

3.2. Treatment

The median number of treatment cycles was 4.0 in the VG arm (range, 0–14) and 5.5 in the CG arm (range, 2–10) (Supplementary Table S1). In the VG arm, three patients received no treatment and five received only one cycle. Three of these eight early treatment terminations were deemed to be treatment related: infusion site reaction of vinflunine leading to treatment interruption at cycle 1, death due to febrile neutropenia, and infection after the first cycle. In the control arm, all patients received at least two cycles of treatment. The most common reason for treatment discontinuation was toxicity in the VG arm (50%) and progressive disease in the CG arm (47%). Any event of dose reduction was performed in 83% and 90% of patients in the VG and CG arm, respectively. Dose reduction was more often due to haematological toxicity in the CG arm but more frequently due to infection and constipation in the VG arm. Dose delay occurred in 48% of the patients in the VG arm and 73% of the patients in the CG arm (Supplementary Table S2).

3.3. Efficacy

In the ITT population, there was no significant difference between the VG and CG arms for the primary endpoint PFS (HR = 0.75, 95% CI: 0.44–1.28; $p = 0.29$) (Fig. 2A): 6.2 months for VG versus 6.3 months for CG. In addition, OS was similar between the two groups: 12.5 months for VG versus 10.7 months for CG (HR = 1.08, 95% CI: 0.60–1.93; $p = 0.81$) (Fig. 2B). Furthermore, in the per-protocol population, there were no significant differences in PFS or OS between the treatment arms as shown in Table 2.

The ORR was higher in the VG arm than in the CG arm (63% versus 40%, respectively) but was not statistically significant in the ITT analysis (Table 2). Furthermore, the VG arm showed a high complete response (CR) rate, i.e. 22% versus 3% in the CG arm. In the per-protocol group, both ORR and CR were significantly higher for VG than for CG ($p = 0.037$ and $p = 0.026$, respectively). The median duration of response in the ITT population was 7.8 months in the VG arm and 8.4 in the CG arm (Fig. 3B). All responses were confirmed except in two patients with partial response (PR).

In the VG arm, the primary tumour was a target lesion in three patients; all responded to treatment (one with CR and two with PR). Moreover, eight patients had the primary tumour registered as non-target lesion (three in VG and five in the CG arm). With respect to

Table 1
Baseline clinical characteristics of the intention-to-treat population.

Characteristic	Vinflunine /gemcitabine (n = 32)	Carboplatin /gemcitabine (n = 30)
Sex		
Male	24 (75)	20 (67)
Female	8 (25)	10 (33)
Median age, years (range)	71 (50–84)	74 (43–82)
ECOG performance status		
0	17 (53)	12 (40)
1	15 (47)	18 (60)
Median creatinine clearance, ml/min (range)	43 (30–55)	47 (32–57)
30–40 ml/min	8 (25)	5 (17)
40–60 ml/min	24 (75)	25 (83)
Primary tumour		
Bladder	20 (63)	22 (73)
Renal pelvis	9 (28)	6 (20)
Ureter	2 (6)	2 (7)
Unknown location[a]	1 (3)	0
Disease extent		
Advanced locoregional[b]	1 (3)	2 (7)
Metastatic	30 (94)	28 (93)
Unknown extent[a]	1 (3)	0
Visceral metastases	18 (56)	18 (60)
Only non-visceral metastases	14 (44)	12 (40)
Metastatic site		
Locoregional recurrence	8 (25)	6 (20)
Regional lymph nodes	17 (53)	13 (43)
Distant lymph nodes	14 (44)	12 (40)
Lung	11 (34)	9 (30)
Liver	5 (16)	7 (23)
Bone	1 (3)	9 (30)
Other	5 (16)	3 (10)
Unknown sites[a]	1 (3)	0
Prior locoregional curative treatments		
Cystectomy/nephrectomy	21 (66)	20 (67)
Radiotherapy	0	2 (7)
Prior neoadjuvant chemotherapy	1 (3)	5 (17)
Prior adjuvant chemotherapy	0	1 (3)
Median time since perioperative chemotherapy, months	7.7	18.5

ECOG, Eastern Cooperative Oncology Group.
Data are n (%), except where noted.
[a] Baseline data missing because of stroke before onset of treatment (one patient).
[b] Primary T4bN0M0 (one patient), locoregional recurrence only (two patients).

the location of the primary tumour (upper urinary tract versus bladder tumours), no clear differences in efficacy were observed (Supplementary Table S4).

3.4. Safety and health-related quality of life

Overall, 59 patients received at least one treatment cycle and were evaluated for safety, in accordance with the protocol. AEs are summarised in Table 3. The most common AEs were haematological toxicities, fatigue, gastrointestinal disorders and nausea/vomiting.

The most common grade III/IV haematological AEs were neutropenia (62% in VG and 43% in CG) and thrombocytopenia (7% in VG and 37% in CG). Febrile neutropenia occurred more often in the VG arm (31%) than in the CG arm (7%). One patient in the VG group died due to infection secondary to treatment-induced febrile neutropenia (grade V). Considering all patients, the majority (90%) of the non-haematological AEs were grade I/II. Renal toxicity was uncommon, with 14% in the VG arm and 7% in the CG group, and no grade III/IV.

HRQoL was assessable in 90% of the patients at baseline and in 58% of the patients after two treatment cycles. There were no statistical differences between the VG and CG arms in any of the HRQoL variables at baseline or after two cycles (Supplementary Table S3). Moderate clinical differences (10–19 points) favouring the control arm were found for physical functioning, role functioning, fatigue and diarrhoea. Small clinical differences (5–9 points) in the same direction were

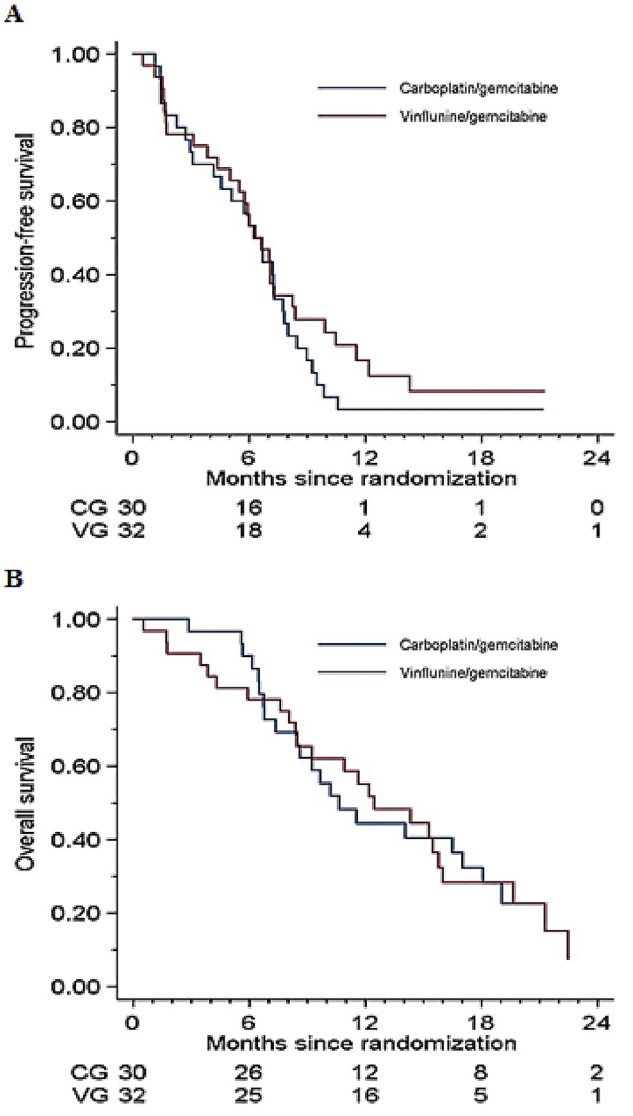

Fig. 2. Efficacy in the intention-to-treat population. (A) Progression-free survival. (B) Overall survival. VG, vinflunine and gemcitabine; CG, carboplatin and gemcitabine.

Table 2
Efficacy variables in the intention-to-treat and per-protocol populations.

Efficacy variable	Intention-to-treat			Per-protocol[a]		
	Vinflunine /gemcitabine $n = 32$	Carboplatin /gemcitabine $n = 30$	HR and/or p-value	Vinflunine /gemcitabine $n = 29$	Carboplatin /gemcitabine $n = 30$	HR and/or p-value
Median PFS, months (95% CI)	6.2 (4.4–8.3)	6.3 (4.2–7.8)	HR 0.75 (0.44–1.28) $p = 0.293$	6.6 (5.0–8.2)	6.3 (4.2–7.8)	HR 0.71 (0.41–1.22) $p = 0.210$
Median OS, months (95% CI)	12.5 (8.4–15.8)	10.7 (7.4–17.0)	HR 1.08 (0.60–1.93) $p = 0.810$	14.3 (9.2–16.0)	10.6 (7.4–17.0)	HR 0.95 (0.52–1.75) $p = 0.879$
Response						
Complete response	7 (22)	1 (3)	$p = 0.054$	7 (24)	1 (3)	$p = 0.026$[a]
Partial response	13[b] (41)	11 (37)	$p = 0.799$	13[b] (45)	11 (37)	$p = 0.601$
Stable disease	3 (9)	12 (40)	$p = 0.007$[a]	2 (7)	12 (40)	$p = 0.005$[a]
Progressive disease	5 (16)	6 (20)	$p = 0.746$	5 (17)	6 (20)	$p = 1.000$
Not evaluable	4 (13)	0	$p = 0.114$	2 (7)	0	$p = 0.237$
Overall response rate	20[b] (63)	12 (40)	$p = 0.126$	20[b] (69)	12 (40)	$p = 0.037$[a]
Disease control rate	23[b] (72)	24 (80)	$p = 0.558$	22[b] (76)	24 (80)	$p = 0.761$

PFS, progression-free survival; CI, confidence interval; HR, hazard ratio; OS, overall survival; AE, adverse event.
HR is calculated with the log-rank test, and p-value, with the Fisher exact test.
Data are represented as n (%), except where noted.
*Statistically significant, $p < 0.05$.
[a] Two patients were excluded because of AE before onset of treatment; one patient withdrawn because of infusion site reaction at first cycle.
[b] Two patients with partial response did not have confirmed responses.

found between the treatment groups for global health status, social functioning, nausea and vomiting and constipation.

4. Discussion

The VINGEM trial is the first randomised study to compare VG treatment with standard CG as first-line therapy for patients with aUC ineligible for cisplatin due to renal impairment. After the present trial was designed, immunotherapy was approved as first-line treatment for cisplatin-unfit patients with aUC. Although immunotherapy has shown impressive and durable responses, the ORR is less than 25% for pembrolizumab and atezolizumab [9,10]. Recently, the EMA and Food and Drug Administration restricted the indication for first-line use of both of these checkpoint inhibitors to patients with high PD-L1 expression; for the non-high PD-L1 expressing population, approximately 70% of the patients [11], chemotherapy with CG remains recommended standard treatment, and further development of more efficacious regimens represents an unmet medical need [20].

The present trial included patients with favourable performance status ($\leq$1) and with renal impairment as the only criterion necessary to be considered ineligible for cisplatin treatment. The median PFS and OS observed in the VG arm were not significantly improved compared with the control arm, although they were similar to what was shown in the JASINT1 trial [16], which applied the same criteria as used in the present study to define cisplatin ineligibility. In our study, there were eight early treatment terminations in the VG arm but none in the control arm, although only three of these eight terminations were deemed to be treatment related. Thus, eight of 32 patients in the VG arm received only 0 or 1 cycle of treatment, which may have affected the survival outcomes and interpretation of the overall efficacy in the ITT population.

Although ORR was not the primary end-point in this study, the high response rate of 63% observed in the VG arm, including 22% CR rate, was notable. This response rate exceeds the numbers reported for other chemotherapy regimens in unfit patients, e.g. the phase III trial CG vs M-CAVI [5] (including the subgroup treated with CG unfit to cisplatin only due to impaired renal function, ORR 47%, CR 6%), the JASINT1 trial [16] and vinflunine in second-line treatment [14,15]. The response rate in our trial is comparable with the best response data reported for cisplatin-based chemotherapy in aUC [3,21,22]. In the per-protocol population, ORR and CR rate differed statistically significantly between the treatment arms in favour of VG. Interestingly, there were also apparent inter-individual> variations in efficacy within the VG arm. As demonstrated in Fig. 3A, several patients showed durable PR and CR, whereas other subjects seemed *de novo* resistant.

Overall, side-effects in both treatment arms were manageable. However, AEs were more frequently reported in the VG arm, although this was not reflected as any detectable significant differences in HRQoL. Haematological toxicity was comparable with what has previously been reported for VG [16] and CG [5]. However, grade III/IV neutropenia for VG was more common in the present study than in the JASINT1 trial [16] (62% versus 38%) but was similar to previously reported incidences for CG [5] and for vinflunine as

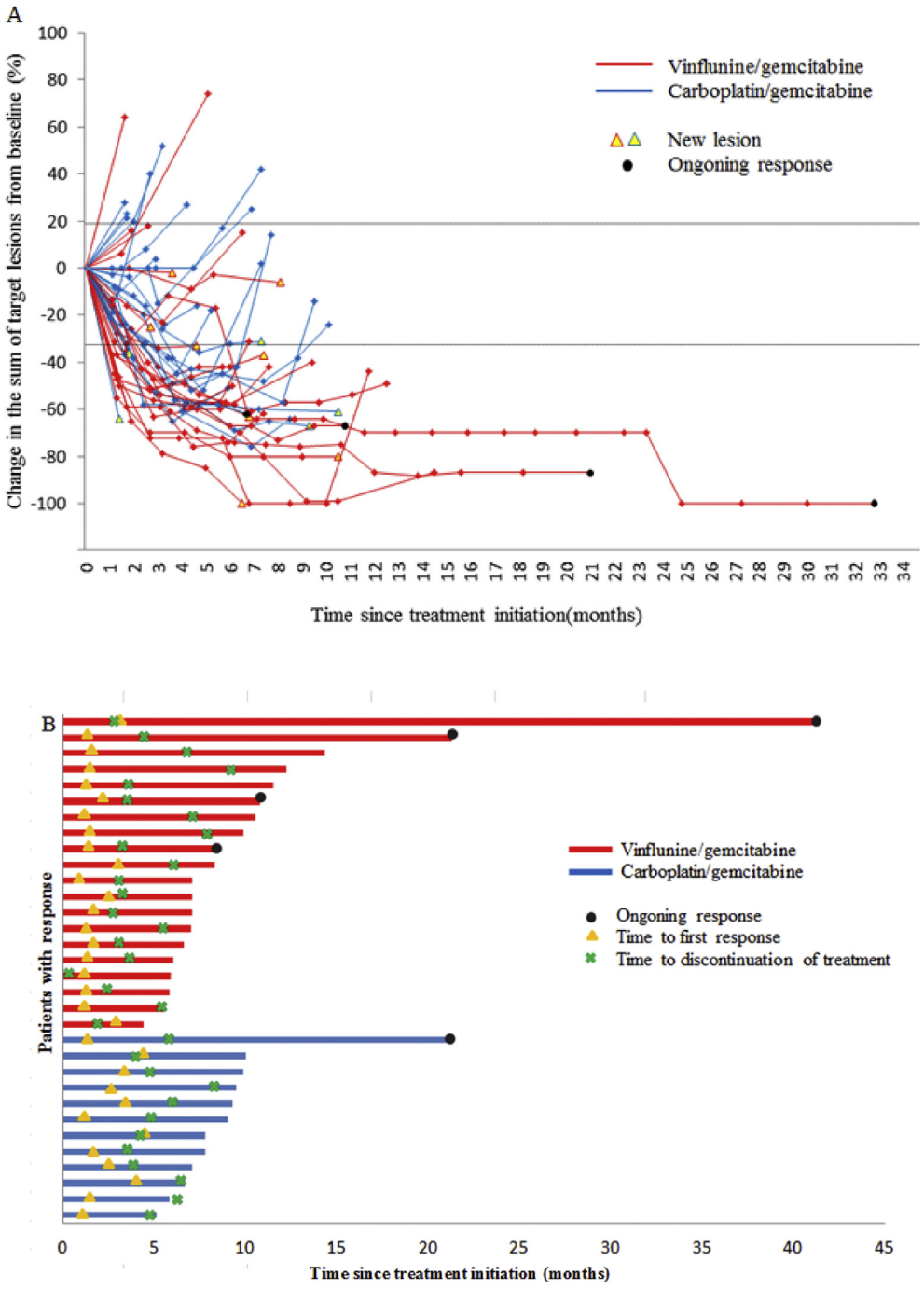

Fig. 3. (A) Percentage change in sum of target lesion diameters from baseline over time. Patients with only non-target lesions are excluded. The diagram illustrates, according to RECIST, version 1.1, progression at 20% (upper dotted line) and response at 30% (lower dotted line). (B) Time to response and duration of response in patients with objective response according to RECIST, version 1.1. Bars indicate the duration of response at the time of data cut-off. RECIST, Response Evaluation Criteria in Solid Tumours.

monotherapy in the post-platinum setting [14]. Moreover, a high rate of infection and febrile neutropenia was observed in the VG arm, including one febrile neutropenia-related death. In the JASINT1 trial, the start dose for gemcitabine was 750 mg/m^2, with possibility to escalate to 1000 mg/m^2 in cycle 2. Nonetheless, the dose was increased for only 52% of the patients, and thus, the lower incidence of neutropenia and febrile neutropenia observed in the JASINT1 trial may be at least partly explained by administration of a lower median dose of gemcitabine. In view of the observed toxicity in the present trial, in particular, the high incidence of neutropenia and associated febrile neutropenia, adjusted doses and treatment schedules or the addition of G-CSF

Table 3
Adverse events (AEs)[a].

Adverse event	Vinflunine/gemcitabine, $n = 29$[b]		Carboplatin/gemcitabine, $n = 30$	
	All grades	Grade III/IV	All grades	Grade III/IV
Haematological AE (predefined)				
Anaemia	17 (59)	4 (14)	20 (67)	8 (27)
Neutropenia	18 (62)	18 (62)	18 (60)	13 (43)
Febrile neutropenia	–	9[c](31)	–	2 (7)
Thrombocytopenia	11 (38)	2 (7)	14 (47)	11 (37)
Thrombocytopenia with active bleeding	1 (3)	0	3 (10)	1 (3)
Non-haematological AE (predefined)				
Constipation	16 (55)	1 (3)	6 (20)	0
Abdominal pain	9 (31)	1 (3)	3 (10)	0
Fatigue	25 (86)	1 (3)	23 (77)	3 (10)
Nausea	13 (45)	1 (3)	11 (37)	2 (7)
Vomiting	9 (31)	0	2 (7)	0
Stomatitis/mucositis	14 (48)	1 (3)	8 (27)	0
Musculoskeletal disorders, pain	7 (24)	2 (7)	9 (30)	2 (7)
Infusion site reactions	7 (24)	0	3 (10)	0
Renal toxicity	4 (14)	0	2 (7)	0
Peripheral neuropathy	5 (17)	0	6 (20)	0
Alopecia	15 (52)	–	3 (10)	–
Dehydration	2 (7)	2 (7)	0	0
Fever	7 (24)	1 (3)	3 (10)	0
Infection	9 (31)	5 (17)	5 (17)	2 (7)
Other AEs, (not predefined)[d]				
Anorexia/weight loss	11 (38)	0	7 (23)	0
Diarrhoea	7 (24)	0	4 (13)	1 (3)
Dyspnoea	3 (10)	0	1 (3)	0
Oedema limbs	3 (10)	0	1 (3)	0
Skin reactions (including pruritus, rash)	4 (14)	0	4 (13)	1 (3)

Data are represented as n (%), except where noted.
[a] Possibly treatment-related AEs in at least one arm.
[b] Two patients were excluded because of AE before onset of treatment; one patient withdrawn because of infusion site reaction at first cycle.
[c] One patient died because of febrile neutropenia, grade V.
[d] Possibly related AEs in at least one arm in ≥10% of patients.

in a putative curative perioperative setting should be considered in future trials evaluating VG.

The treatment landscape of aUC is rapidly expanding, including several ICIs [23], targeted therapies such as inhibitors of fibroblast growth factor receptor family (FGFR) [24] and antibody-drug conjugates targeting nectin-4 [25]. In this era of several conceptually different treatment strategies, there is an unmet need of robust predictive biomarkers to optimise patient selection and treatment sequence. PD-L1 expression has been suggested as a predictive biomarker for treatment with ICIs, but is controversial due to different analytical methods and its significance is still unclear in both first- and second-line treatment in aUC [23]. Furthermore, besides being a potential predictive biomarker, PD-L1 expression may also be a prognostic marker for patients treated with ICIs or chemotherapy [23,26,27]. Hence, it would be of interest to evaluate the PD-L1 expression in relation to the outcomes of VG as well. Since ICIs appear to be non-efficient in cisplatin-ineligible aUC-patients with low PD-L1 expression, efficacious treatment options in this population remain an unmet need. Although the toxicity profile must be taken into consideration, VG may be an effective and feasible alternative to CG in patients with good performance status and preserved bone marrow function.

This study has several limitations. The trial was initially planned for 120 patients but was downsized due to slow accrual rate, which reduces the statistical power and the probability of demonstrating significant differences between the treatment arms. Furthermore, there was an imbalance between the treatment arms considering the number of patients that had received perioperative chemotherapy, which may influence sensitivity to study treatment and the efficacy outcome. In addition, a randomised phase II screening trial design requires verification of positive findings in a subsequent phase III trial.

5. Conclusions

In this trial, first-line treatment with VG did not improve PFS compared with standard carboplatin-based treatment in patients with aUC considered cisplatin-unfit due to renal impairment. However, the experimental VG arm did show notable activity, with an ORR and a CR rate comparable with the best response

rates previously reported for any systemic therapy in aUC. Moreover, the VG regimen was generally tolerable and had an expected side-effect profile, albeit with a high frequency of neutropenia and febrile neutropenia. Future studies are warranted to identify biomarkers specific for the VG combination and to address inter-individual differences in efficacy in the context of molecular taxonomy and PD-L1 expression. Furthermore, it may also be of interest to explore the VG regimen in the neoadjuvant setting for patients with impaired renal function or as backbone in combination with immunotherapy or targeted drugs.

Conflict of interest statement

K.H. declares receiving speaker honoraria from Roche AB and Ipsen. L.S.M. has served the role of a consultant, has been a member of the advisory board for MSD and reports receiving reimbursement for travel, accommodations and meeting expenses from MSD, Roche, Pfizer, BMS, Janssen and Astellas. H.P. has received research grants from MSD and Roche, has been a member of the advisory board in MSD Denmark and has received speaker honoraria for BMS. A.U. has received research grants from Swedish Cancer Society, Stockholm County Council, the Cancer Society in Stockholm, King Gustaf V Jubilee Fund, Sanofi-Aventis, Bayer and Pierre Fabre; reports receiving speaker honoraria and has been a member of the advisory board for Pierre Fabre, Amgen, Roche, Pfizer, Janssen-Cilag and MSD. All remaining authors have declared no conflicts of interest.

Funding

This trial was an academic study supported by grants from the Swedish Cancer Society (grant agreement #160718 and #160762), the Cancer Society of Stockholm (grant agreement #141433, #174303) and the Stockholm County Council (grant agreement #20160051) and was funded by Pierre Fabre Pharma Norden AB through an investigator-initiated research grant (no grant number applicable). The Pierre Fabre company had no influence on the design or performance of the trial, and was not involved in the reporting or interpretation of the data.

Acknowledgements

The authors thank the patients who participated in this trial and their families. The authors are also grateful to all investigators and the study teams at the participating centres. The authors thank the Clinical Trial Unit at Karolinska University Hospital, especially Anita Björk as study monitor and Claudia Maes for coordinating data management.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.033.

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